Rate and Mode of Death during Five Years of Follow-up among Patients with Acute Chest Pain with and without a History of Diabetes Mellitus

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In order to determine the effect of diabetes on the mortality rate and mode of death during 5 years of follow-up among patients who came to the emergency department with acute chest pain or other symptoms suggestive of acute myocardial infarction (AMI), all patients thus presenting to one single hospital during a period of 21 months were followed for 5 years. In total 5230 patients were included, of whom 402 (8 %) had a history of diabetes. Patients with diabetes differed from those without by being older, having a higher prevalence of previously diagnosed cardiovascular diseases, having less symptoms of chest pain and more symptoms of acute severe heart failure, and more electrocardiographic (ECG) abnormalities on admission. Diabetic patients had a 5-year mortality of 53.5 % as compared with 23.3 % among non-diabetic patients ($p < 0.001$; adjusted risk ratio 1.60; 95% confidence limits 1.35–1.90). Among diabetic patients the following appeared as independent predictors of death: age ($p < 0.001$), ST-segment elevation on admission ($P < 0.001$), a history of myocardial infarction ($p < 0.05$), and a non-pathological ECG on admission ($p < 0.001$). We conclude that among diabetic patients admitted to the emergency department with acute chest pain or other symptoms suggestive of AMI more than 50 % are dead 5 years later. Future research should focus on interventions in order to reduce their mortality. © 1998 John Wiley & Sons, Ltd.

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Introduction

Patients with diabetes mellitus have an increased risk of coronary artery disease[1,2] and increased mortality and morbidity after acute myocardial infarction (AMI).[3–6] Many patients present to the emergency department with acute chest pain or other symptoms raising a suspicion of AMI,[7] and although many have ischemic heart disease, only a minority will develop AMI.[8] Few studies have described the prognosis among diabetic patients admitted to the emergency department due to acute chest pain or other symptoms raising suspicion of AMI. We have previously reported the outcome during 1 year of follow-up for such patients.[9]

This study reports the rate and mode of death during 5 years of follow-up in diabetic and non-diabetic patients admitted to the emergency department with acute chest pain or other symptoms raising a suspicion of AMI.

Patients and Methods

Sahlgrenska University Hospital in Goteborg, Sweden, serves a population of about 230 000 inhabitants. All patients admitted to the emergency department between 15 February 1986 and 9 November 1987, with chest pain or other symptoms indicative of AMI, were registered consecutively.

Information on previous history of cardiovascular disease was based on patient interviews and information from patients' medical case books. We did not specifically ask whether they had Type 1 or Type 2 diabetes. We classified the reasons for admission to the emergency department as one or more of the following: chest pain, acute heart failure, arrhythmia, loss of consciousness, or 'other symptoms'.

On the basis of history, clinical examination and a standard 12-lead electrocardiogram (ECG) recorded soon after admission, all patients were classified by the physician on duty into one of the following four categories:

1. Obvious myocardial infarction: typical symptoms and ST-elevation with or without Q-waves on the ECG.

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2. Strongly suspected myocardial infarction:
   (a) typical symptoms but no ST-elevation or Q-waves on the ECG;
   (b) atypical symptoms but ST-segment elevation or ST-segment depression or T-wave inversion or Q-waves on the ECG;
   (c) sudden onset of severe congestive heart failure without ST-elevation or Q-waves on the ECG;
   (d) unstable angina pectoris regardless of the ECG.
3. Vague suspicion of myocardial infarction: difficulties in interpretation of the symptoms and no signs of acute ischaemia on the ECG.
4. No suspected myocardial infarction:
   (a) no suspected ischaemic heart disease;
   (b) stable angina pectoris.

A standard 12-lead ECG was registered soon after admission to the emergency department and classified the following day into one of the following groups by an experienced member of our study group: normal (no pathological signs); pathological, but no signs of acute ischaemia (e.g. old infarctions, bundle branch block, non-specific ST-T changes); or signs of acute ischaemia (ST elevation ≥ 2 mm in leads V1–V4 or ≥ 1 mm in aVL, aVF, I, II, III, V5–V6; ST depression ≥ 1 mm; T-wave inversion; Q wave ≥ 2 mm deep) in at least two leads.

For the diagnosis of a confirmed myocardial infarction, two of the following criteria had to be fulfilled: chest pain with a duration of at least 15 min; serum aspartate aminotransferase levels above the normal range in samples from at least 2 different days, together with elevation of serum creatine kinase; appearance of new Q waves in at least two leads on a 12-lead standard ECG.

For the diagnosis of myocardial ischaemia the criteria were: ST-T-wave changes in the ECG but no elevation of serum enzymes. For the diagnosis of possible myocardial ischaemia a suspicion of myocardial ischaemia was required in the absence of ECG and enzyme elevation.

Evaluation of Cause of Death, Symptoms Associated with Death, and Autopsy Findings

Information on deaths after discharge from hospital was obtained from the Swedish National Registry of Deaths. From this registry, information about all deaths in Sweden is available within 2 weeks after the date of death. In the case of patients who died in hospital, we used their case record forms, including findings at autopsy, for information about the manner of death. In the case of the patients who died outside the hospital, we used information from death certificates, autopsy findings, and sometimes police investigations. The cause of death was defined as cardiac, non-cardiac or uncertain. In a few patients, both cardiac and non-cardiac factors were judged to contribute to death. Cardiac death included death caused by confirmed or possible myocardial infarction and/or if any of the following were described in relation to the time of death: symptoms of congestive heart failure or cardiogenic shock, ventricular fibrillation, pulseless electrical activity, primary asystole, cardiac tamponade, ventricular septal rupture, papillary muscle rupture, or death related to the time of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. The remaining deaths were judged as non-cardiac if a specific diagnosis could be given. The symptoms associated with death were those observed during the last hours or last minutes before death.

Regarding symptoms associated with death, congestive heart failure was defined according to clinical signs and symptoms such as auscultatory rales, severe dyspnoea or pulmonary oedema. Cardiogenic shock was defined as systolic blood pressure < 80 mmHg with simultaneous signs of poor peripheral circulation including oliguria, and if the cause of shock was judged as being of cardiac origin. Ventricular fibrillation and pulseless electrical activity were defined according to traditional criteria.

Follow-up

All patients were approached with a questionnaire where they were asked about smoking habits 1 year after admission to hospital. The response rate was 82 % for diabetic patients and 81 % for non-diabetic patients (NS).

Statistical Methods

Pitman's non-parametric test was used.[10] In the evaluation of proportions Fisher's exact test was used. A p-value < 0.05 was regarded as significant. Two-tailed tests were used. In the multivariate analysis Cox proportional hazards model was used. In univariate analysis with regard to mortality and mode of death p-values are given adjusted to differences in age according to Mantel's technique of pooling applied to Fisher's permutation test; in the Tables 1–7 p-values are denoted if < 0.05.

Results

In all, 5362 patients made 7157 visits to the emergency department due to chest pain or other symtoms suggestive of AMI during the study period. This analysis only includes the first visit for each patient. Among those 5362 patients, information on a history of diabetes was lacking in 10 patients (0.2 %). For the remaining 5352 patients, 412 (8 %) had a history of diabetes. Information on survival was missing in 10 of the diabetic patients (2.4 %) and in 112 of the non-diabetic patients (2.2 %). The study population included these patients in whom information on survival was available.

Previous History

Patients with a history of diabetes were older and had a higher prevalence of previous myocardial infarction,

angina pectoris, hypertension, and congestive heart failure but smoked less frequently than non-diabetic patients (Table 1). Among the diabetic patients who smoked at admission to hospital and were alive after 1 year, 29 % had stopped smoking at that time. The corresponding figure for non-diabetic patients was 25 % (NS). The distribution of sex did not differ between diabetic and non-diabetic patients.

Presentation

Patients with diabetes more frequently had a strong or a vague suspicion of AMI and less frequently no suspicion of AMI as compared with non-diabetic patients (Table 1). They had chest pain less frequently and severe heart failure more frequently as the initial symptom than non-diabetic patients, and were more likely to have a pathological ECG particularly with regard to a pathologic ECG *without* signs of acute ischaemia.

Table 1. Previous history and findings in the emergency department

	Diabetes ($n = 402$)	No diabetes ($n = 4828$)	$p <$
Age (years)			
Median mean ± SD	72, 71 ± 11	64, 60 ± 18	0.001
Range	33–96	16–101	
Sex (%)			
Men	51	56	
Women	49	44	
History of (%)			
Myocardial infarction (2,8)[a]	31	15	0.001
Angina pectoris (1,19)	54	27	0.001
Hypertension (0,1)	43	21	0.001
Congestive heart failure (0,0)	34	11	0.001
Smoking (72,13)	21	35	0.001
Suspicion of AMI (categories) (0,0)			
Category 1	6	5	
Category 2	32	18	0.001
Category 3	40	33	0.01
Category 4	23	45	0.001
Initial symptoms (0,0)			
Chest pain	89	93	0.01
Acute severe heart failure	10	3	0.001
Arrhythmia	7	5	
Loss of consciousness	6	5	
Other symptoms	16	14	
ECG on admission (5,131)			
Normal	23	55	0.001
Pathologic but no signs of acute ischemia	54	26	0.001
Signs of acute ischaemia	23	19	
ST-elevation	9	8	
ST-depression	12	7	0.01
T-wave inversion	6	7	
Q-wave	3	3	

[a]The numbers of patients with missing information for each group are given in parentheses.

Table 2. Medication at hospital discharge

	Diabetic patients (%)	Non-diabetic patients (%)	$p <$
Beta-blockers (315,4548)[a]	45	27	0.001
Calcium antagonists (314,4547)	18	8	0.001
Long-acting nitrates (315,3548)	27	13	0.001
Diuretics (315,4551)	48	25	0.001
Digitalis (315,4549)	31	13	0.001
ACE inhibitors (307,4368)	4	1	0.001
Aspirin (307,4368)	7	5	
Anticoagulants (315,4546)	11	7	0.05
Anti-arrhythmics (315,4546)	4	2	0.05
Lipid lowering drugs (315,4546)	0.3	0.2	
Psychoparmaca (315,4546)	11	10	

[a]Number of patients in whom information was available.

Medication at Discharge

Table 2 shows the proportion of patients being prescribed various medications at discharge from hospital. Diabetic patients were more frequently prescribed beta-blockers, calcium channel blockers, long-acting nitrates, diuretics, digitalis, ACE inhibitors, anticoagulants and anti-arrhythmics than patients without diabetes.

Five-year Mortality

Overall, the 5-year mortality was 53.5 % among diabetic patients as compared with 23.3 % among non-diabetic patients (Figure 1).

The relative difference in mortality between diabetic and non-diabetic patients was similar in various subsets

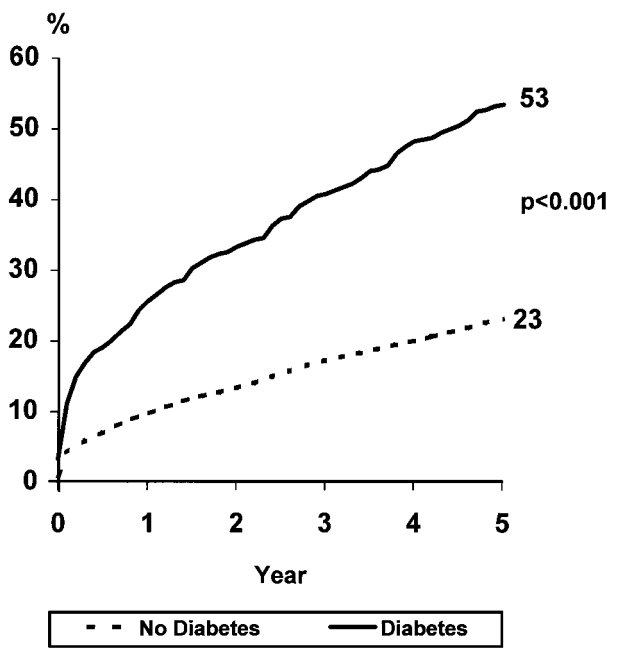

Figure 1. Five-year mortality in diabetic and non-diabetic patients; *p*-value calculated with Pitman's test

according to age, sex, and history of cardiovascular disease. The exception was patients with a history of congestive heart failure, in whom the mortality appeared to be similar in diabetic and non-diabetic patients (Table 3).

When evaluating patients according to initial symptoms, ECG pattern and degree of suspicion of AMI (Table 4), diabetic patients had a higher mortality than non-diabetic patients in all subsets with the exception for patients who had symptoms of acute severe heart failure. In this subset no difference was found between the two groups.

The mortality during initial hospitalization was 13 % among diabetic patients and 7 % among non-diabetic patients ($p < 0.001$). Among diabetic patients who survived to discharge those who were prescribed insulin had a 5-year mortality of 40 % as compared with 37 % for those who were not prescribed insulin (NS). Only 30 % of the diabetic patients were prescribed insulin at discharge.

Multivariate Analysis

In a multivariate analysis (Table 5) where all factors listed in Table 1 were included in the model, a history of diabetes appeared as a significant predictor of death (risk ratio 1.60; 95 % confidence limits 1.35–1.90; $p < 0.0001$). In addition to a history of diabetes the following appeared as significant predictors of death: age, male sex, symptoms of acute congestive heart failure or unspecific symptoms on admission, smoking, a history of either congestive heart failure, previous myocardial infarction or hypertension, initial degree of suspicion of AMI and presence of pathological ECG on admission to hospital.

When a second multivariate analysis among patients discharged alive from hospital was performed, adding those medications listed in Table 2 which were significantly associated with 5-year mortality in univariate analysis (beta-blockers, long-acting nitrates, diuretics, digitalis, ACE inhibitors, and aspirin) to the previously defined independent predictors of death, a history of diabetes remained as a significant predictor of death (risk ratio 1.58; 95 % confidence limits 1.29–1.95; $p < 0.0001$).

Among patients with a history of diabetes the following appeared as independent predictors of death: greater age, ST-elevation on admission, and a history of previous myocardial infarction. A normal ECG on admission was associated with improved survival.

Table 3. Five-year mortality in relation to clinical history

	Diabetic patients		Non-diabetic patients		$p <$[a]
Age (years; quartiles)					
1 (16–48 years)	2/16	12.5	28/1295	2.2	
2 (49–64 years)	34/94	36.2	145/1207	12.0	
3 (65–75 years)	68/143	47.6	366/1256	29.1	
4 (76–101 years)	111/149	74.5	586/1071	54.7	
Sex					
Males	99/204	48.5	644/2695	23.9	0.001
Females	116/198	58.6	481/2133	22.6	0.001
Previous history of:					
Myocardial infarction					
Yes	74/123	60.2	318/729	43.6	0.001
No	139/277	50.2	804/4092	19.6	0.001
Angina pectoris					
Yes	118/217	54.4	468/1305	35.9	0.001
No	96/184	52.2	646/3505	18.4	0.001
Hypertension					
Yes	94/172	54.6	349/993	34.4	0.001
No	121/230	52.6	783/3835	20.4	0.001
Congestive heart failure					
Yes	93/138	67.4	330/543	60.8	
No	122/264	46.2	795/4286	18.6	0.001
Smoking					
Yes	32/69	46.4	269/1204	22.3	0.01
No	144/262	55.0	596/2278	26.2	0.001

[a] *p*-value adjusted for differences in age.

Mortality in Relation to Final Diagnosis

Patients were re-evaluated 1 year after the index event and given a final diagnosis as the cause of the index event. In Table 6 diabetic patients are compared with non-diabetic patients in various subsets according to final diagnosis.

Mode of Death

Diabetic patients who died differed from non-diabetic patients who died by more frequently suffering a cardiac death and more frequently dying from a myocardial infarction (Table 7). Furthermore, they more frequently died in association with congestive heart failure and less frequently died at home.

Revascularization

Among diabetic patients 8 % underwent coronary artery bypass grafting during 5 years of follow-up as compared with 4 % among non-diabetic patients. The corresponding figures for percutaneous transluminal coronary angioplasty were 1 % and 1 %, respectively.

Discussion

In this study evaluating patients coming to the emergency department with acute chest pain or other symptoms raising suspicion of AMI, we found that 8 % had a history of diabetes mellitus. This figure is higher than in a general unselected population without coronary artery disease[11] but lower than among patients developing AMI.[3,4]

The observation that diabetic patients had a higher

Table 4. Five-year mortality in relation to initial symptoms, ECG pattern, and suspicion of AMI

	Diabetic patients		Non-diabetic patients		$p <$[a]
Initial symptoms					
Chest pain	186/357	52.1	975/4491	21.7	0.001
Acute congestive heart failure	28/41	68.3	109/156	69.9	
Arrhythmia	20/29	69.0	78/255	30.6	0.001
Syncope	13/22	59.1	76/223	34.1	0.05
Other symptoms	40/63	63.5	177/670	26.4	0.001
Initial ECG pattern					
Normal	22/92	23.9	238/2564	9.3	0.05
Pathologic but no signs of acute ischemia	130/213	61.0	529/1240	42.7	0.001
Signs of acute ischaemia	61/93	65.6	340/912	37.3	0.001
ST-elevation	28/36	77.8	148/389	38.0	0.001
ST-depression	31/49	63.3	154/343	44.9	0.05
T-wave inversion	15/24	62.5	112/346	32.4	
Q-wave	11/13	84.6	67/143	46.8	
Initial suspicion of AMI					
Category 1	16/22	72.3	96/228	42.1	0.01
Category 2	77/127	60.6	339/845	40.1	0.001
Category 3	85/161	52.8	415/1576	26.3	0.001
Category 4	37/92	40.2	275/2180	12.6	0.001

[a]*p*-value adjusted for differences in age.

Table 5. Independent predictors for 5-year mortality ($n = 325$)

Predictors	Risk ratio	95 % CL[a] Lower	Upper	$p <$
Age	1.05	1.04	1.07	0.001
ECG on admission				
Normal	0.38	0.21	0.66	0.001
ST-elevation	2.48	1.61	3.82	0.001
Previous history of:				
Myocardial infarction	1.42	1.03	1.95	0.05

[a]CL, confidence limit.

prevalence of previous cardiovascular diseases than non-diabetic patients is well described.[3,4,12,13] In previous studies dealing with patients having ischaemic heart disease, female sex is usually over-represented among diabetic patients with ischaemic heart disease as compared with non-diabetic patients.[4] However, in our group of non-selected patients with acute chest pain or other symptoms raising suspicion of AMI, the distribution of sex was similar in diabetic and non-diabetic patients.

We found that diabetic patients more often had other symptoms than chest pain raising suspicion of AMI. One suggested explanation is that diabetic patients often have autonomic neuropathy which might result in less chest

Table 6. Five-year mortality in relation to final diagnosis

	Diabetes Number	%	No diabetes Number	%	$p <$[a]
Ischaemic heart disease					
Definite AMI	74/95	77.9	344/708	48.6	0.001
Possible AMI	20/31	64.5	64/167	38.3	
Myocardial ischaemia	17/49	34.7	104/378	27.5	
Possible myocardial ischaemia	52/98	53.1	223/812	27.5	0.001
No ischaemic heart disease					
Pulmonary embolism	2/6	33.3	14/48	29.2	
Pleuropneumonia	9/17	52.9	49/182	26.9	
Gastritis, ulcus, oesophagitis	3/10	30.0	34/260	13.1	
Pericarditis	0		2/55	3.6	
Hepatobiliar disease	0/2	0	8/36	22.2	
Musculoskeletal pain	4/22	18.2	71/699	10.2	
Psychogenic pain	2/8	25.0	29/420	6.9	
Other cause of pain	28/50	56.0	187/616	30.4	0.001
Uncertain cause of pain	13/33	39.4	87/755	11.5	0.001

[a]*p*-value adjusted for differences in age.

Table 7. Place and mode of death during 5 years of follow-up

	Diabetes $n = 215$ %	No diabetes $n = 1125$ %	$p <$[a]
Place of death			
At home	12	18	0.05
At work	0	0.1	
In ambulance	0.9	0.5	
In emergency department	0.9	2	
In coronary care unit	25	20	
In other hospital ward	57	56	
In another place	4	4	
Cause of death			
Cardiac	78	63	0.001
Acute myocardial infarction	47	32	0.001
Possible myocardial infarction	6	4	
Non-cardiac	42	50	
Stroke	10	7	
Pulmonary embolism	4	3	
Uncertain	8	8	
Symptoms associated with death			
Congestive heart failure	40	31	0.05
Cardiogenic shock	9	8	
Ventricular fibrillation	7	5	
Pulseless electrical activity	6	6	
Witnessed death	88	83	
Death ≤ 1 hour after onset of symptoms	17	18	
Death ≤ 24 hours after onset of symptoms	45	55	
Autopsy findings			
Autopsy rate	37	39	
Fresh myocardial infarction	66	45	0.01
Cardian tamponade	6	7	

[a]*p*-value adjusted for differences in age.

pain during myocardial ischemia.[14,15] The diabetic patients more often had a pathologic ECG on admission, either with or without signs of myocardial ischemia, which to some extent might explain why there was a stronger suspicion of AMI in diabetic than in non-diabetic patients in the emergency department.

We found that among patients with acute chest pain or other symptoms raising suspicion of AMI, diabetic patients had a mortality during the subsequent 5 years that was more than twice that of non-diabetic patients and the history of diabetes mellitus was a strong independent predictor of death. This observation is in agreement with many previous studies.[3–6,16–19] Four independent predictors for an adverse prognosis were found among the diabetic patients. That high age was related to an increased mortality was not unexpected as previous studies in patients, with and without a history of diabetes, age has been shown to be an independent predictor of death in ischaemic heart disease.[20,21] Previous myocardial infarction has also been associated with an adverse prognosis among patients with ischaemic heart disease before[22,23] and ST segment elevation, known to predict development of AMI,[8] was also not a surprising association of adverse outcome, as most of these patients did develop AMI.

A normal ECG on admission to hospital was an independent predictor for an improved prognosis. Although such an observation has not been demonstrated among diabetic patients with acute chest pain before, the value of the initial ECG in order to select high and low risk groups is well known[24,25] but has not previously been demonstrated in diabetic patients with acute chest pains.

In this study, a history of diabetes was based on patient interviews and information from medical records rather than biochemical markers and we did not prospectively classify patients into Type 1 and Type 2 diabetes. Long-term prognosis was related to information based on clinical parameters. Neither residual ischaemia nor signs of arrhythmias, with the exception for ventricular fibrillation and treated ventricular tachycardia were assessed and we have no information of ejection fraction. The rate of revascularization procedures and use of thrombolytic agents, aspirin, ACE inhibitors, and lipid lowering drugs was low in 1986–87 and it may be that some of these treatments affect the long-term prognosis.

However, we have demonstrated that the 5-year mortality among diabetic patients coming to the emergency department with acute chest pain or other symptoms raising suspicion of AMI is over 50 %. Predictors of

death can be found in the emergency department as reflected in age, initial electrocardiographic pattern, and a history of myocardial infarction and these simple factors may be useful in targeting therapeutic intervention to those at highest risk in future.

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